October 29, 2001

Donald W. Lamb, Ph.D.
Vice President
Product Safety & Regulatory Affairs
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-9741

Dear Dr. Lamb,

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Cyclohexyl isocyanate (CAS No.3173-53-3), transmitted to EPA May 3, 2001. I commend Bayer Corporation for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

The Company supplied a Test Plan that proposed the reduced suite of testing permitted for a "closed system intermediate." However, as explained in our comments, we do not believe that Bayer has adequately supported that claim. For instance, the criteria for "closed system intermediates" apply to ALL sites in the U.S. Also, beyond a broad statement claiming that the chemical must be handled in closed systems because of its reactivity, there is little of the supporting information required by the applicable guidance document. EPA generally agrees with the other aspects of the Test Plan as noted in our comments.

Regarding the issue of testing "closed system intermediates," EPA has asked that sponsors observe a number of principles included in a letter to sponsor companies dated October14, 1999 (http://www.epa.gov/chemrtk/ceoltr2.htm). The guidance is relevant to your proposal because participants are asked to defer animal testing on individual chemicals until 2003 if a test substance is a "closed system intermediate." It is the intention of the Agency that the HPV Challenge Program should proceed in a manner consistent with this guidance.

The Company needs to supply information missing from the ecotoxicity and acute toxicity robust summaries.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that Bayer advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
C. Auer
M. E. Weber
A. Abramson

EPA Comments on Chemical RTK HPV Challenge Submission: Cyclohexyl isocyanate

SUMMARY OF EPA COMMENTS

The sponsor, Bayer Corporation, submitted a Test Plan to EPA, transmitted May 3, 2001, for Cyclohexyl isocyanate (CAS No.3173-53-3). EPA posted the submission on the ChemRTK HPV Challenge Web site on July 3, 2001.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data. EPA agrees with the test plan for these endpoints. The information from the water stability test at pH 7, such as identification of hydrolyzed products and half-life, is crucial for review of ecological effects.

2. Health Endpoints. Existing oral data are adequate for acute toxicity. The sponsor will conduct testing to address the other SIDS endpoints except for repeat dose and reproductive toxicity. The sponsor asserts that these two endpoints do not need to be addressed because cyclohexyl isocyanate is a "closed system intermediate." However, EPA does not agree that this claim has been adequately supported (see specific comments below).

3. Ecotoxicity. One environmental effects study was provided; however, since cyclohexyl isocyanate hydrolyzes rapidly in water, the sponsor noted that cyclohexylamine (a hydrolysis product of cyclohexyl isocyanate) is a more appropriate test substance. Robust summaries on tests available for this substance should be provided if the proposed hydrolysis testing bears this out. In addition, if 1,3-dicyclohexylurea (CAS No. 2387-23-7) is a significant hydrolysis product, testing on this chemical should also be provided.

EPA requests that the Sponsor advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE CYCLOHEXYL ISOCYANATE CHALLENGE SUBMISSION

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

EPA agrees with the sponsor's test plan for these endpoints.

Environmental Fate (photodegradation, stability in water, biodegradation, and transport/distribution).

EPA agrees with the sponsor's test plan for these endpoints. The proposed hydrolysis test will determine if cyclohexylamine is the principal degradation product and thus whether available ecotoxicity data on this chemical can be used to address the ecotoxicity endpoints. If the rate is so fast as to preclude testing according to the guideline (OECD 111), the sponsor should give some indication of the half-life: "seconds" or "minutes." Also, the sponsor should consider doing the transport/distribution modeling on cyclohexylamine, the presumed principal hydrolysis product.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The sponsor submitted six summaries for acute toxicity (two each for oral, dermal, and inhalation routes). Although missing some study details the two oral studies taken together satisfy the acute toxicity endpoint. The two inhalation tests were not acceptable as they were designed to determine time-to-death (LC100) at high test concentrations of 7,160 or 13,524 mg/m^3. The dermal studies were not adequately summarized

so that the study quality cannot be determined from the available information, and the reported minimal lethal doses from each study were significantly different.

The sponsor proposes testing to address genetic and developmental toxicity. No testing is proposed for repeat dose and reproductive toxicity because the sponsor claims that cyclohexyl isocyanate qualifies for the reduced testing allowed for "closed system intermediates."

The Guidance for Testing Closed System Intermediates for the Challenge Program http://www.epa.gov/chemrtk/guidocs.htm allows for a reduced testing proposal provided certain criteria are met. The information required to judge a "closed system intermediate" claim must address the following:

I. Site information.
   A. Number of sites.
   B. Basis for "closed process" conclusion at each site.
      1) Process description.
      2) Monitoring data showing no detection.
      3) In the absence of monitoring data, the basis for believing that releases do not occur.
   C. Data on "presence in distributed products."

II. Information on transport (mode, volume, controls, etc.)

III. A data search showing that the chemical is not present in other end-products.

Other than a general statement about the reactivity of cyclohexyl isocyanate and the need to manufacture and transport the chemical under controlled "closed" conditions, the criteria above have not been adequately addressed. For instance, there is no discussion about whether all sites in the U.S. manufacture and handle the chemical in a manner consistent with the definition of a "closed system intermediate." There is no process description, discussion of presence or absence of monitoring data, or information on transport. Although, given the reported reactivity of the chemical and its stated use, there is probably little likelihood of its presence in other products, the supporting data are lacking. Consequently, EPA does not agree that the claim for reduced testing because of "closed system intermediate" status is supported by the information presented in the Test Plan.

Ecological Effects.

The sponsor identified rapid hydrolysis to cyclohexylamine as the possible fate of cyclohexyl isocyanate. The sponsor noted that "since there are many studies on fish, Daphnia, and algae using cyclohexylamine, it is believed that these endpoints will be filled with that data." If the hydrolysis product is indeed cyclohexylamine and the rate of hydrolysis is rapid (as determined by the stability in water test), the sponsor plans no additional environmental effects studies. This approach is acceptable, assuming that the sponsor will submit test data for the amine and other degradation products that may form (e.g., 1,3-dicyclohexylurea, 2387-23-7). An alternative approach would be to test cyclohexyl isocyanate itself, because all of the hydrolysis products would be present in the water and the results would be representative of the toxicity of hydrolyzed cyclohexyl isocyanate.

Among the most important considerations is the stability of the test substance: recommended test conditions depend on the hydrolysis half-life value. Information related specifically to the testing of hydrolysis half-life also appears under "Alkoxysilanes" in the document "TSCA New Chemicals Program (NCP): Chemical Categories," available at www.epa.gov/oppt/newchems/chemcat.htm. While this guidance was developed for a different purpose, it contains useful technical information. Thus, in order to evaluate the adequacy of the ecotoxicity data for cyclohexyl isocyanate, it is essential to have reliable stability in water (hydrolysis) data.

SPECIFIC COMMENTS ON ROBUST SUMMARIES

Fate

Biodegradation

The use of an emulsifier should only be done when absolutely necessary, and in any case it should be selected carefully so it does not itself biodegrade under the conditions of the test. Otherwise, at a level of 1g/L (very high), it seems that biodegradation of the additive would swamp that of the test substance. The sponsor should clarify this issue.

Transport and Distribution (Fugacity)

The sponsor should provide the input values it used for its estimation of the Level III Fugacity model.

Health Effects

Acute toxicity. Two acute studies were provided for each route of exposure (oral, dermal, and inhalation).

Two robust summaries were submitted for acute oral toxicity studies in rats. Neither test used a standard guideline method. Of the information provided in the summaries, the methods and results were described in adequate detail. However, the summaries lack the following information: no. of doses, no. of animals per dose, no. of dead animals per dose, no. of animals per dose showing clinical signs, and GLP status. Given the available data and that the LD_{50} values are similar, the summaries taken together are considered adequate for this endpoint.

For dermal toxicity, two robust summaries were submitted. Neither test used a standard guideline method. The summaries are considered inadequate because of limited descriptions of methods and results. The study summaries lack the following information: no. of doses (ok for the second study Ref. 5), no. of animals per dose, no. of dead animals per dose, no. of animals per dose showing clinical signs, and GLP status. Minimal Lethal Doses (MLDs) from each study appeared to be substantially different (500 vs. 2000-3260 mg/kg).

Two robust summaries were submitted for acute inhalation toxicity studies in rats. Both of these studies were designed to determine the time-to-death (LC100) following exposure to saturated air concentrations of the test material (the method for calculating the test chamber concentrations was not adequately described). In one study summary (Ref. 5), only limited data were provided on gross effects of exposure and information on macroscopic evaluation was not provided. These studies were considered to be inadequate to describe the effects of acute inhalation exposure to cyclohexyl isocyanate.

Ecotoxicity Studies

Fish. One summary was submitted for acute toxicity of cyclohexyl isocyanate to fish. The 72-hour LC_0 for *Leuciscus idus* in this range-finding static test was inadequate for this endpoint because a 96-hour LC50 test is the standard measure of toxicity. Furthermore, the summary did not provide sufficient study information regarding the chemical tested, concentrations tested, water conditions, loading, or control data.

Followup Activity

EPA requests that the Sponsor advise the Agency within 60 days of any modifications to its submission.